REMARKS/ARGUMENTS

This is intended to be a complete response to the Office Action mailed December 27, 2007, in which claims 8 and 19-23 were rejected. Applicant has amended claims 8 and 19 herein. Claims 1-7 and 9-18 have been cancelled without prejudice in a previous amendment submitted on October 16, 2007. Claims 8 and 19 - 23 remain pending in this application.

Information Disclosure Statement

The Examiner noted that Reference AX on the information disclosure statement filed November 30, 2004 was not provided and was not considered.

Applicant apologizes for this clerical error and has submitted a supplemental information disclosure statement enclosing the AX Reference herewith.

Applicant's Response to the Objection to the Specification

In the Office Action dated December 27, 2007, the Examiner stated:

> "The specification is objected to because it does not comply with the Sequence Rules. 37 CFR 1.821(c) requires that each sequence that appear in the specification being assigned a sequence identification number, i.e. SEQ ID NO. However, in the instant specification the same sequence is being assigned two SEQ ID NOs. For example, SEQ ID NO: 2 (617

amino acids) is 100% identical to SEQ ID NO: 4 (617 amino acids)."

Applicant's representative thanks the Examiner for pointing out the clerical error in the sequence listing. SEQ ID NO: 2 and SEQ ID NO: 4 are amino acid sequences of two proteins with a single amino acid substitution from Threonine to Isoleucine at position 455. Adequate support is provided in the specification at paragraph [0044]. Also as evident from the originally filed Sequence Listing, their corresponding nucleic acid sequences, SEQ ID NO: 1 and SEQ ID NO: 3, respectively, feature a single nucleotide substitution from cytosine (C) to thymine (T) at position 1364.

Applicant's representative apologizes for this clerical error and has submitted an amended sequence listing herewith. Applicant respectfully submits that the amendment to SEQ ID NO: 4 is fully supported by the specification and SEQ ID NO: 3 in the originally filed Sequence Listing. Therefore, this amendment does not constitute new matter. Entry of the substitute Sequence Listing is respectfully requested.

Also in the Office Action, the Examiner stated:

"The specification is objected to because it recites GenBank accession "AF438904" (e.g., page 14, [0038]) wherein the correct number is "AF439804"."

Applicant thanks the Examiner for pointing out the typographic error in the GenBank accession number in the specification; the specification has been amended to change "AF438904" to "AF439804".

Therefore, Applicant respectfully requests that the objections to the specification be reconsidered and withdrawn by the Examiner.

Applicant's Response to the 35 U.S.C. § 112 ¶ 1 Rejection

In the Office Action, the Examiner rejected claims 8 and 19-23 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. In support of the rejection, the Examiner stated that:

> While there is support in the specification for sequences that are 70% identical to SEQ ID NOs: 12 or 14 (page 23, [0055]), i.e., to the nucleic acid sequences, the examiner is unable to locate adequate support in the specification for sequences that are 70% identical to SEQ ID NOs: 13 or 15, i.e., to the amino acid sequences.

Applicant respectfully traverses the rejection. Applicant respectfully submits that the specification of the current application provides a full and adequate description of amino acid sequences that are at least 70% identical to SEQ ID NO: 13 and 15. The Examiner's attention is directed to the following citations from the Specification as originally filed:

(1) Paragraph [0010]: "In the presently claimed and disclosed invention, pmHS1 and pmHS2 (**approximately 70% identical at the amino acid level**) are identified";

(2) Paragraph [0012]: "It is an object of the presently claimed and disclosed invention to provide a purified nucleic acid segment comprising at least one of: . . . (d) a purified nucleic acid segment encoding an enzymatically active, soluble heparin synthase, wherein the enzymatically active, soluble heparin synthase is **at least 70% identical to SEQ ID NO:13 or 15** (emphasis added)"; and

(3) Paragraph [0014]: "It is another object of the presently disclosed and claimed invention . . . to provide a purified nucleic acid segment comprising at least one of: . . . (i) a purified nucleic acid segment encoding a modified heparin synthase . . . **at least about 70% identical to SEQ ID NO:**2, 4, 6, **13, 15** or 34 (emphasis added)".

Thus, Applicant respectfully submits that there is more than adequate support in the written description of the Specification as originally filed for "a soluble heparin synthase having an amino acid sequence that is at least 70% identical to at least one of SEQ ID NO: 13 or 15", and therefore such term

does not constitute new matter. Applicant respectfully requests that reconsideration and withdrawal of this rejection.

Also in the Office Action, the Examiner rejected claims 8 and 19-23 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

Applicant respectfully traverses the rejection. However, in order to expedite prosecution, items (E) and (F) in independent claims 8 and 19 have been cancelled, without prejudice. Thus, it is respectfully requested that the Examiner reconsider and withdraw the rejection of claims 8 and 19-23 under 35 U.S.C. § 112, first paragraph.

Also in the Office Action, the Examiner rejected claims 8 and 19-23 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

In support of the rejection, the Examiner stated that:

> the specification ... does not reasonably provide enablement for methods of use of heparin synthase ... having at least 70% identity to SEQ ID NOs: 13 or 15 or encoded by a DNA that hybridizes to SEQ ID NOs: 12 or 14 under hybridization conditions recited in clause "(D)" of claims 8 and 19 . . .

Applicant respectfully traverses the rejection based on the reasons stated herein below.

In the specification of the present application, Applicant clearly demonstrates production of four full-length heparin/heparosan synthases (two pmHS1 with GenBank Accession Nos. AF425591 and AF439804, and two pmHS2 with GenBank Accession Nos. AY292199 and AY292200), and three soluble heparin/heparosan synthases, $pmHS1^{K45M-617}$, $pmHS1^{I77M-617}$, and thioredoxin fused wild type pmHS1. Applicant respectfully submits that the disclosure of these species constitutes adequate disclosure of a genus of heparin/heparosan synthases, and therefore Applicant should not be limited to the specific sequences disclosed therein but rather should be entitled to claims directed to the genus. Applicant has offered two ways that are typically acceptable to the Office for claiming such genus: the first method of claiming such genus is through the use of percent identity to the disclosed sequences; the second is through the use of hybridization language and specific hybridization conditions are included in the claims as a limitation.

The Examiner has argued that undue experimentation is required to practice the invention as claimed by these methods; however, Applicant respectfully traverses these assertions.

The Examiner first asserts that the specification does not establish which regions of the protein structure may be modified without affecting heparin synthase activity; however, Applicant respectfully submits that a person having ordinary skill in the art would clearly recognize that the

portions of pmHS2 (represented by SEQ ID NOS: 6 and 34) that were not identical to the equivalent portions of pmHS1 (represented by SEQ ID NOS:2 and 4) are regions of the protein structure that may possibly be modified without affecting heparin/heparosan synthase activity. In addition, the motifs of SEQ ID NOS: 22 and 23 clearly demonstrate portions of the protein structure that cannot be modified without affecting heparin/heparosan synthase activity (i.e., amino acids 118-193 and 421-513 of SEQ ID NOS: 2 and 4, as recited in the motifs of SEQ ID NOS: 22 and 23, cannot be modified without affecting heparin/heparosan synthase activity).

Furthermore, the subject application also describes the production of pmHS1 mutants that are single action, i.e., a GlcUA-transferase or a GlcNAc-transferase (see Published application, Page 12, paragraph [0089] through Page 14, Table VIII). The GlcUA-transferase, $pmHS1^{D444N-D446N}$(SEQ ID NO:27), contains only two amino acid substitutions when compared to the wild type pmHS1 sequence. Likewise, the GlcNAc-transferase, $pmHS1^{D181N-D183N}$ (SEQ ID NO:25), also only contains two amino acid substitutions when compared to the wild type pmHS1 sequence. Therefore, the disclosure of these two single action mutants clearly demonstrates four amino acids within the protein that are absolutely critical to the dual-action transferase activity of the heparin/heparosan synthase (i.e., amino acids 118, 183, 444, and 446 of SEQ ID NOS: 2 and 4).

In addition, the alignments shown in Figure 1 and 3 contain consensus lines that clearly illustrate conserved and semi-conserved amino acids between (1) the heparin/heparosan synthases of the present invention and the *E. coli* KfiA and KfiC proteins, which are single transferase enzymes that work together to synthesize heparin (Fig. 1); and (2) the two heparin/heparosan synthases of the presently disclosed and claimed invention, pmHS1 and pmHS2 (Fig. 3). Such alignments and consensus lines, when combined with the other disclosures discussed herein, provide adequate guidance to a person having ordinary skill in the art as to (1) residues that are conserved between these proteins, and thus are more than likely not tolerant to modification; (2) residues that are not conserved between these proteins and that would be candidates for modifications that would still retain activity; and (3) portions of the protein that are responsible for the UDP-GlcUA or UDP-GlcNAc transferase activity of the protein.

Therefore, based on the disclosures of the present application discussed above, Applicant respectfully submits that the specification clearly establishes regions of the protein structure which may be modified without affecting heparin/heparosan synthase activity, as well as a rational and predictable scheme for modifying residues in heparin/heparosan synthases with an expectation of obtaining the desired biological function.

The Examiner also asserted that the specification does not establish "the general tolerance of heparin synthases to modification and extent of such tolerance", and refers to the Townsend et al. prior art reference. The Townsend et al. reference teaches an incorrect sequence due to a sequencing error that resulted in a frame-shift mutation. However, the present invention actually demonstrates that the protein taught by Townsend et al. is not active, and such disclosure actually provides much guidance on the extent of the modification of the sequences of SEQ ID NOS:2 and 4; that is, the negative teachings of the protein of Townsend et al. would provide clear guidance to a person having ordinary skill in the art as to portions of SEQ ID NOS:2 and 4 that cannot be modified without affecting heparin/heparosan synthase activity (i.e., more than amino acids 1-497 of SEQ ID NOS: 2 and 4 are required to maintain activity of the protein).

The Examiner also stated that the specification does not establish "a rational and predictable scheme for modifying any residues in heparin synthases with an expectation of obtaining the desired biological function"; again, Applicant respectfully traverses this assertion based on the same arguments presented above.

The Examiner also stated that "the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be

successful". Again, Applicant respectfully submits that the sequences and alignments disclosed in the subject application provide a person of ordinary skill in the art with the required reasonable amount of guidance to practice the presently claimed invention. While the Examiner has asserted there are "essentially infinitely possible choices", Applicant respectfully directs the Examiner's attention to Ex parte Chen (61 USPQ2nd (BNA) 1025, 2000 WL 33671755 (Bd. Pat. App & Inteferences 2000), in which it was recognized that the success rate for practicing the invention taught therein was low (~1%), but in which the Board stated that "the numbers emphasized by the Examiner would reasonably appear to reflect the need for a repetitive procedure, rather than undue experimentation". Further, in In re Certain Limited-Charge Cell Microcarriers (221 USPQ (BNA) 1165, 1174, 1983 WL 54215 (Int'l Trade Comm'n 1983), it was held that if "the art typically engages in such experimentation", even if it may be "complex", it is "not necessarily undue". Applicant respectfully submits that such is the case with the presently claimed invention: the specification of the subject application provides adequate and reasonable guidance to a person having ordinary skill in the art, who is versed in hybridization experimentation and detection of percent sequence identity, to perform routine experimentation in the art to identify nucleic acid segments, recombinant vectors and recombinant host cells that meet the limitations of the claims of the subject application.

In support of the rejection, the Examiner cites In re Wands (858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir., 1988), which lays out factors to be considered in determining whether undue experimentation is required. However, Applicant would also like to direct the Examiner's attention to Page 1404 of In re Wands, where the court explained that "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed". Applicant respectfully submits that the specification of the subject application provides such reasonable amount of guidance (as outlined above) to enable a person having ordinary skill in the art to identify nucleic acid segments, recombinant vectors and recombinant host cells that meet the limitations of the claims of the subject application.

In addition, Applicant respectfully directs Examiner's attention to several other patents that have issued in which Applicant is a co-inventor. Such patents are directed to hyaluronan synthase (HAS), which is another glycosaminoglycan transferase. These patents were granted under similar circumstances, i.e., the work being the first identification and cloning of a single protein that is a dual action transferase that catalyzes the addition of UDP-GlcUA and UDP-GlcNAc to form hyaluronan. US Patent Nos. 7,060,469; 7,060,466; 7,029,880; 7,026,159; 6,991,921; 7,141,409; 7,115,405;

7,109,011; and 7,087,413 contain claims directed to purified nucleic acids encoding HAS, recombinant host cells encoding HAS, recombinantly produced or isolated enzymatically active HAS, methods of producing HA and using HAS, and methods of elongating a functional acceptor using HAS, wherein the HAS is not limited specifically to a particular sequence but rather is defined by hybridization-type language, motif-type language, or simply as "a single protein that is a dual-action catalyst that utilizes UDP-GlcUA and UDP-GlcNAc to form hyaluronan". Thus, Applicant is simply attempting to obtain similar patent protection for the heparin/heparosan synthase enzymes that he has identified, and respectfully submits that he is entitled to such patent protection.

Therefore, Applicant respectfully submits that the specification of the subject application fully enables the invention as claimed without requiring undue experimentation.

Also in the 35 U.S.C. 112, first paragraph, enablement rejection, the Examiner stated that "the specification ... does not reasonably provide enablement for ... a method for elongating the acceptor without a divalent ion".

In response to the rejection, independent claim 19 has been amended to add the limitation of "at least one divalent metal ion suitable for synthesis of a heparin/heparosan polymer", a limitation already present in claim 8. As

the Examiner indicated that "the specification enables for a method for elongating the functional acceptor using the enzymes of the instant invention in the presence of a divalent ion", Applicant respectfully submits that currently amended claim 19, as well as dependent claims 20-23, are enabled.

In view of the above arguments, it is respectfully requested that the Examiner reconsider and withdraw the rejection of claims 8 and 19-23 under 35 U.S.C. § 112, first paragraph.

Applicant's Response to the 35 U.S.C. § 112 ¶ 2 Rejection

In the Office Action, the Examiner rejected claims 8 and 19-23 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Claims 8 and 19 have been amended to change "a complement" to "the complement" to correct a typographic error. Support in the specification can be found in paragraph [0055], where sequences which are essentially the same as those set forth in SEQ ID NO: 12 or 14 are functionally defined as sequences which are capable of hybridizing to a nucleic acid segment containing **the complement** (emphasis added) of SEQ ID NO: 12 or 14 under standard or less stringent hybridizing conditions.

Claims 8 and 19 have been amended to change "heparin synthase" to "heparin/heparosan synthase" to clarify that both heparin and heparosan (unmodified heparin) are polymers having the β4GlcUA-α4GlcNAc backbone, as defined in paragraph [0005].

Claim 18 has been amended to remove reference to "UDP sugar analogs".

In view thereof, it is respectfully requested that the Examiner reconsider and withdraw the rejection of claims 8 and 19-23 under 35 U.S.C. § 112, second paragraph.

Applicant's Response to the 35 U.S.C. § 102 Rejection

In the Office Action, the Examiner rejected claims 8 and 19-23 under 35 U.S.C. 102(b) as being anticipated by DeAngelis *et al.* Applicant respectfully traverses the rejection for the reasons stated herein below.

The present invention is directed to a method for producing a heparin/heparosan polymer ***in vitro*** using a **soluble** heparin/heparosan synthase.

DeAngelis *et al.* teach a **full-length, membrane-associated** heparosan synthase from *Pasteurella multocida* encoded by the nucleic acid sequence with GenBank Accession No. AF425591, which is 100% identical to SEQ ID NO: 1 disclosed in the specification of the present invention.

However, the presently disclosed and claimed invention is not directed to a **full length** heparin/heparosan synthase that is membrane-associated. Rather, the presently disclosed and claimed invention relates to a **soluble** heparin/heparosan synthase. In contrast to the membrane-associated protein, soluble heparin/heparosan synthase is easy to purify, and the expression level thereof can be increased without overloading the membrane while still retaining enzymatic activity (see paragraph [0054]).

Furthermore, the truncations of pmHS1 that resulted in a soluble protein will not be apparent to one of ordinary skill in the art since, as already disclosed in paragraph [0084] of the specification, 1) the location of the truncations are opposite to the prediction based on a similar protein, pmHAS hyaluroran synthase (i.e., carboxyl terminus truncations conferred solubility to pmHAS, whereas amino terminus truncations were required to confer solubility to pmHS1); and 2) existing computer programs for predicting transmembrane segments or membrane associations or hydrophobicity plots failed to predict that the amino terminal region is the membrane associated region of a heparin/heparosan synthase.

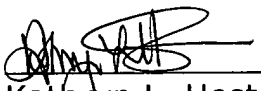
In view of the above remarks, it is submitted that all pending claims are patentably distinguished over the cited prior art. Thus, it is respectfully requested that the Examiner reconsider and withdraw the rejection of claims 8 and 19-23 under 35 U.S.C. § 102 and pass the pending claims to issuance.

CONCLUSION

This is meant to be a complete response to the Office Action mailed December 27, 2007. Applicant respectfully submits that each and every rejection of the claims has been overcome. Furthermore, Applicant respectfully submits that claims 8 and 19-23, as now pending, are in a condition for allowance. Favorable action is respectfully requested.

Should the Examiner have any questions regarding this amendment, or the Remarks contained therein, Applicant's representative would welcome the opportunity to telephonically discuss the same with the Examiner.

Respectfully submitted,



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